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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/526,106	03/15/2000	Robert F. Balint	PARE.002.01US	9164

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/526,106	BALINT ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20031110*.
4) ☒ Interview Summary (PTO-413) Paper No(s). *20040124*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

1. The Response filed November 3, 2003 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 63-66 were pending. Applicants amended claims 63-66. Therefore, claims 63-66 are currently pending and examined on the merits.

Election/Restriction

4. Applicants previously elected amino acid sequence (corresponding to amino acids 1-197 in SEQ ID NO. 2 wherein said fragment comprises the amino acid substitution (c) a methionine to threonine at position 182, see attached interview summary in Paper No. 24) has been interpreted to include only amino acids 26-197 (with the methionine → threonine mutation still occurring at position 182) in light of the obvious numbering mistake. Please note that if this interpretation is not correct then the Examiner contends that Applicants' current November 3, 2003 amendment would not be in compliance because none of Applicants' currently pending claims would encompass an amino acid sequence that is 197 amino acids long (e.g., 207-26 =

181 i.e., <198 amino acids, see claim 63). Confirmation in writing is respectfully requested by Applicants to make the record clear.

Withdrawn Objections/Rejections

5. All previous objection and/or rejections are withdrawn in view of Applicants' amendments and/or arguments.

New Rejections

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 63-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject mater which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (New Matter).

For example, newly amended claim 63 recites an N-terminal β-lactamase fragment with the sequence shown wherein "at least one" amino acid substitution is made selected from the group consisting of steps (a), (b) or (c). Example 7 provides two examples of substitution including K55E/M182T and P62S/M182T using α197. However, the Examiner does not find support for any of the other mutations (e.g., K55E/M182T/P62S using α207) that would fall

within the scope of this claim (see also, Example 7, page 48, lines 5-6, "An exhaustive search for more mutations did not turn up any mutants with interaction-dependent activity").

7. Claims 63-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabled for non-mutant N-terminal β-lactamase fragments that are used in complementation systems that contain an NGR tri-peptide, a $(Gly_4Ser)_3$ linker and a C-terminal β-lactamase fragment are not enabling for mutant N-terminal β-lactamase fragments (e.g., $55_{Lys \rightarrow Glu}$, $62_{Pro \rightarrow Ser}$ and $182_{Met \rightarrow Thr}$ mutations) that are used in complementation systems that contain any C-terminal fragment and any linker and any tri-peptide or other variant. This is an enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) Breadth of the claims and nature of the invention: The scope of the claim is broad because Applicant uses "comprising" terminology that would include an infinite

number of sequences. Furthermore, applicants' claims encompass mutating said infinite number of sequences (e.g., $55_{Lys \rightarrow Glu}$, $62_{Pro \rightarrow Ser}$ and $182_{Met \rightarrow Thr}$ mutations) and using said infinite number of sequences in undisclosed complementation systems.

(3 and 5) The state of the prior art and the level of predictability in the art: The prior art teaches that protein aggregation, folding and binding interactions are inherently unpredictable. It is known in the art that even a single amino acid change can have dramatic effects on the proteins' structure/function. For example, Voet et al. (1990) teach that a single Glu → Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic and blood flow blockages (see Voet, D. and Voet, J. G. Biochemistry. New York: John Wiley and Sons 1995, pages 126-128, section 6-3A and page 230, column 2, first paragraph). Here, Applicants' "comprising" language would include the addition of "amino acids" to the N- and/or C-terminal end of the fragment, which would have an unpredictable effect on the structure/function of the fragment. Furthermore, another layer of unpredictability would be added onto this by the claimed mutations (e.g., e.g., $55_{Lys \rightarrow Glu}$, $62_{Pro \rightarrow Ser}$ and $182_{Met \rightarrow Thr}$ mutations).

In addition, the prior art indicates that the claimed β-lactamase enzyme fragment would not function with all "complementation systems" i.e., only complementation systems that contain Asn-Gly-Arg tripeptide (NGR) and the $(Gly_4Ser)_3$ linker in addition to the complementary C-terminal β-lactamase fragment would be enabled (e.g., see

Wehran et al, Abstract, "Critical to this advance [describing Applicants' claimed invention as exemplified in Example 6 of the specification] was the identification of a tri-peptide, Asn-Gly-Arg [NGR], which when juxtaposed at the carboxyl terminus of the α fragment increased complemented enzyme activity by up to 4 orders of magnitude") (emphasis on the word "critical") (Wehrman, T.; Kleaveland, B.; Her, J.-H.; Balint, R.F.; blau, H.M. "Protein-protein interactions monitored in mammalian cells via complementation of β-lactamase enzyme fragments" PNAS 2002, 99(6), 2469-3474). In this regard, it is noted that claims which lack critical or essential subject matter, which is necessary to the practice of the invention, but is not included in the claim(s), including essential compound structure, is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976); and *Ex Part Bhide* (Bd Pat. App. & Int.) 42 USPQ2d 1441.

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants disclose only examples of "non-mutant" N-terminal β-lactamase fragments that contain "interaction-dependent" activity (e.g., see Example 6 in specification). Furthermore, these "non-mutant" N-terminal β-lactamase fragments are coupled to essential tri-peptides like NGR, a $(Gly_4Ser)_3$ linker and a C-terminal β-lactamase enzyme fragment. For example, Applicants state, "However, for both mutants [i.e., referring to combinations of the currently claimed $55_{Lys\rightarrow Glu}$, $62_{Pro\rightarrow Ser}$ and $182_{Met\rightarrow Thr}$ mutations], plating efficiencies were just as high or higher in the absence of

the heterolgous interaction i.e., with the jun helix removed. An exhaustive search for more mutations did not turn up any mutants with interaction-dependent activity. Thus, in contrast to the results obtained with random tri-peptides, where activation remained interaction-dependent, adaptive mutations of α197 invariably eliminated interaction dependents" (see specification page 48, lines 3-8, see more generally Example 7) (emphasis added). Complementation systems, however, require "interaction-dependent" activity because without this activity the complementation system could not differentiate between test proteins that interact with one another from those that do not (e.g., the N-terminal and C-terminal fragments would come together regardless of whether the test proteins interact thus negating the usefulness of the complementation system).

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The Examiner contends that the quantity of experimentation needed to make and or use the invention would be great because Applicants specification provides evidence that the claimed invention will not work (see sections 6-7 above). In addition, Applicants have omitted essential subject matter (see sections 3 and 5 above). Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991).

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D. Epperson, Ph.D. whose telephone number is (703) 308-2423. The examiner can normally be reached on Monday-Friday from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Jon D. Epperson, Ph.D.
January 24, 2004

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